

We Claim.

1. A method to enhance the cytotoxic activity of an antineoplastic drug against
a disorder of abnormal cell proliferation, comprising administering an effective
amount of the antineoplastic drug to a host in need of treatment in combination with
an effective cytotoxicity-increasing amount of an antioxidant.
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2. A method to decrease the toxicity to an antineoplastic agent administered for
the treatment of a solid growth of abnormally proliferating cells, comprising
administering an antioxidant prior to, with, or following the antineoplastic treatment.
3. A method to increase the therapeutic index of an antineoplastic agent
10 administered for the treatment of a solid growth of abnormally proliferating cells,
comprising administering an antioxidant prior to, with, or following the antineoplastic
treatment.
4. A method to increase the nuclear localization of C/EBP β in a cell,
comprising administering an antioxidant to the interior of the cell.
- 15 5. A method to inhibit the carboxymethylation of the catalytic subunit of
protein phosphatase 2A by the methyltransferase which acts on protein phosphatase
2A, comprising contacting methyltransferase with an antioxidant in a sufficient
amount to achieve inhibition.
6. A method for the identification of compounds that increase the cytotoxicity
20 of antineoplastic agents comprising assessing the compound's ability to promote
phosphorylation at Ser²⁹⁹ of C/EBP β .

7. A method for the identification of compounds that increase the cytotoxicity
of antineoplastic agents comprising assessing the compound's ability to inhibit the
carboxymethylation of protein phosphatase 2A.

8. A peptide sequence of the form -X1-Arg-X2-Ser-X3 wherein X2 is the
5 C/EBP- β amino acid at position 298, and X1 and X3 represent flanking peptide
sequences with substantial homology to C/EBP β .

9. The method of claim 1, wherein the abnormal cell proliferation is colorectal
cancer.

10. The method of claim 1, wherein the abnormal cell proliferation is breast
cancer.

11. A protein complex that consists of C/EBP β , PP2A, and the
methyltransferase responsible for PP2A subunit carboxymethylation, in at least 70 /
purity.

12. A method for treating a condition of abnormal cell proliferation in a host,
comprising administering to the host an effective amount of C/EBP β , or a protein with
substantial homology to C/EBP β , in phosphorylated or unphosphorylated form.

13. The method of claim 13, wherein the protein with substantial homology to
C/EBP β consists of or contains a peptide sequence of the form -X1-Arg-X2-Ser-X3
wherein X2 is the C/EBP β amino acid at position 298, and X1 and X3 represent
20 flanking peptide sequences with substantial homology to those of C/EBP β , and
wherein the term substantial homology refers to a protein or peptide sequence that

performs substantially the same function as the parent sequence and has at least 60 % sequence identity.

14. A synthetic C/EBP β analog that has a stabilized phosphate bond or an analog thereof that is resistant to dephosphorylation.

5 15. The synthetic analog of claim 15 that is a phosphoroamidate or phosphonate analog.

16. The method of claim 1, 2, 3, 4, or 5, wherein the antioxidant is a *mild* dithiocarbamate.

10 17. The method of claim 16, wherein the dithiocarbamate is of the structure A-SC(S)-B, wherein A is hydrogen or a pharmaceutically acceptable cation, and B is alkyl, alkenyl, alkynyl, alkaryl, aralkyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, alkaryl, hydrogen, C₁₋₆ alkoxy-C₁₋₁₀ alkyl, C₁₋₆ alkylthio-C₁₋₁₀ alkyl, NR²R³, -(CHOH)_nCH₂OH, wherein n is 0, 1, 2, 3, 4, 5, or 6, -(CH₂)_nCO₂R¹, including alkylacetyl, alkylpropionyl, and alkylbutyryl, or hydroxy(C₁₋₆)alkyl- (wherein one or 15 more hydroxyl groups are located on any of the carbon atoms), or NR²R³, wherein R² and R³ are independently alkyl; -(CHOH)_n(CH₂)_nOH, wherein n is 0, 1, 2, 3, 4, 5, or 6; -(CH₂)_nCO₂R¹, -(CH₂)_nCO₂R⁴; hydroxy(C₁₋₆)alkyl-; alkenyl (including but not limited to vinyl, allyl, and CH₃CH=CH-CH₂.CH₂); alkyl(CO₂H), alkenyl(CO₂H), alkynyl(CO₂H), or aryl, wherein the aryl group can be substituted as described above, notably, for example, with a NO₂, CH₃, t-butyl, CO₂H, halo, or p-OH group; or R² and 20 R³ can together constitute a bridge such as -(CH₂)_m- , wherein m is 3, 4, 5, 6, 7, 8, 9, or 10, and wherein R⁴ is alkyl, aryl, alkaryl, or aralkyl, including acetyl, propionyl, and

butyryl, or wherein B can be a heterocyclic or alkylheterocyclic group, which can be

partially or totally hydrogenated.

18. The method of claim 1, 2, 3, 4, 5, or 6, wherein the antioxidant is probucol

or

5 a mono or diester thereof.

19. The method of claim 18, wherein one or both of the hydroxyl groups of probucol are replaced with esters of succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, or maleic acid.

20. The method of claim 1, 2, 3, 4, 5, or 6 wherein the antioxidant is a 2,6-dialkyl-4-silylphenol.

10 21. The method of claim 1, 2, 3, 4, 5 or 6, wherein the antioxidant is N-acetyl cysteine.

15 22. The method of claim 1, 2, 3, 4, 5 or 6, wherein the antioxidant is selected from the group consisting of a scavenger of peroxide, a thiol, an inhibitor of lipid peroxidation, a dietary antioxidant, inhibitors of lipoxygenases and cyclooxygenases, antioxidants manufactured by the body, and synthetic phenolic antioxidants.

20 23. The method of claim 1, 2, 3, 6, or 7, wherein the antineoplastic agent is selected from the group consisting of Aceglatone; Aclarubicin; Altretamine; Aminoglutethimide; 5-Aminolevulinic Acid; Amsacrine; Anastrozole; Ancitabine Hydrochloride; 17-1A Antibody; Antilymphocyte Immunoglobulins; Antineoplaston A10; Asparaginase; Pegaspargase; Azacitidine; Azathioprine; Batimastat; Benzoporphyrin Derivative; Bicalutamide; Bisantrene Hydrochloride; Bleomycin

Sulphate; Brequinar Sodium; Broxuridine; Busulphan; Campath-IH; Caracemide;

Carbetimer; Carboplatin; Carboquone; Carmofur; Carmustine; Chlorambucil;

Chlorozotocin; Chromomycin; Cisplatin; Cladribine; Corynebacterium parvum;

Cyclophosphamide; Cyclosporin; Cytarabine; Dacarbazine; Dactinomycin;

5 Daunorubicin Hydrochloride; Decitabine; Diaziquone; Dichlorodiethylsulphide;

Didemnin B.; Docetaxel; Doxifluridine; Doxorubicin Hycloride; Droloxifene;

Echinomycin; Edatrexate; Elliptinium; Elmustine; Enloplatin; Enocitabine; Epirubicin

Hydrochloride; Estramustine Sodium Phosphate; Etanidazole; Ethoglucid; Etoposide;

Fadrozole Hydrochloride; Fazarabine; Fenretinide; Flouxuridine; Fludarabine

10 Phosphate; Fluorouracil; Flutamide; Formestane; Fotemustine; Gallium Nitrate;

Gencitabine; Gusperimus; Homoharringtonine; Hydroxyurea; Idarubicin

Hydrochloride; Ifosfamide; Ilmofosine; Imrosulfan Tosylate; Inolimomab;

Interleukin-2; Irinotecan; JM-216; Letrozole; Lithium Gamolenate; Lobaplatin;

Lomustine; Lonidamine; Mafosfamide; Melphalan; Menogaril; Mercaptopurine;

15 Methotrexate; Methotrexate Sodium; Miboplatin; Miltefosine; Misonidazole;

Mitobronitol; Mitoguazone Dihydrochloride; Mitolactol; Mitomycin; Mitotane;

Mitozanetrone Hydrochloride; Mizoribine; Mopidamol; Multialchipeptide;

Muromonab-CD3; Mustine Hydrochloride; Mycophenolic Acid; Mycophenolate

Mofetil; Nedaplatin; Nilutamide; Nimustine Hydrochloride; Oxaliplatin; Paclitaxel;

20 PCNU; Penostatin; Peplomycin Sulphate; Pipobroman; Pirarubicin; Piritrexim

Isethionate; Piroxantrone Hydrochloride; Plicamycin; porfimer Sodium;

Prednimustine; Procarbazine Hydrochloride; Raltitrexed; Ranimustine; Razoxane;

Rogletimide; Roquinimex; Sebriplatin; Semustine; Sirolimus; Sizofiran; Sobuzoxane;
Sodium Bromebrate; Sparfasic Acid; Sparsosate Sodium; Sreptozocin; Sulofenur;
Tacrolimus; Tamoxifen; Tegafur; Teloxantrone Hydrochloride; Temozolomide;
Teniposide; Testolactone; Tetrasodium Mesotetraphenylporphine-sulphonate;
5 Thioguanine; Thioinosine; Thiotepa; Topotecan; Toremifene; Treosulfan;
Trimetrexate; Trofosfamide; Tumor Necrosis Factor; Ubenimex; Uramustine;
Vinblastine Sulphate; Vincristine Sulphate; Vindesine Sulphate; Vinorelbine Tartrate;
Vorozole; Zinostatin; Zolimomab Aritox; and Zorubicin Hydrochloride.

24. The method of claim 1, 2, 3, or 12, wherein the abnormal cell proliferation
10 is a benign tumor.

25. The method of claim 1, 2, 3, or 12, wherein the abnormal cell proliferation
is a malignant tumor.

26. The method of claim 1, 2, 3 or 12, wherein the abnormal cell proliferation
is a hyperproliferative or preneoplastic lesion.

15 27. The method of claim 1, 2, 3 or 12, wherein the abnormal cell proliferation
is selected from the group consisting of papilloma, adenoma, firoma, chondroma,
osteoma, lipoma, hemangioma, lymphangioma, leiomyoma, rhabdomyoma,
meningioma, neuroma, ganglioneuroma, nevus, pheochromocytoma, neurilemma,
fibroadenoma, teratoma, hydatidiform mole, granulosa-theca, Brenner tumor,
20 arrenoblastoma, hilar cell tumor, sex cord mesenchyme, interstitial cell tumor,
thyoma, renal cell carcinoma, prostatic adenocarcinoma, bladder
carcinoma, adenocarcinoma, fibrosarcoma, chondrosarcoma, osteosarcoma,

liposarcoma, hemangiosarcoma, lymphangiosarcoma, leiomyosarcoma,
rhabdomyosarcoma, myelocytic leukemia, erythroleukemia, multiple myeloma,
glioma, meningeal sarcoma, thyoma, cystosarcoma phyllodes, nephroblastoma,
teratoma choriocarcinoma, cutaneous T-cell lymphoma (CTCL), cutaneous tumors
5 primary to the skin or infiltrating the skin, Kaposi's sarcoma, and premalignant and
malignant diseases of mucosal tissues, central nervous system tumors, mycosis
fungoides, psoriasis, dermatomyositis, rheumatoid arthritis, viruses, molluscum
contagiosum, remalignant and malignant diseases of the female genital tract.

28. The method of claim 1, 2, 3 or 12, wherein the abnormal cell proliferation
10 is selected from the group consisting of colorectal cancer, ovarian cancer, bone cancer,
renal cancer, breast cancer, gastric cancer, pancreatic cancer, melanoma, and
hematopoietic tumors.
29. The method of claim 1, 2, 3, or 12, wherein the abnormal cell proliferation
is a cardiovascular condition.
- 15 30. The method of claim 29, wherein the cardiovascular condition is post
angioplasty restenosis.